REMARKS

Claims 1-24 are pending, and claims 21-24 have been withdrawn by the Examiner in view of a restriction requirement.

Applicants thank the Examiner for considering applicants' traversal of the restriction requirement.

The specification has been objected to in view of applicants' prior amendments to the Sequence Listing. Applicants respectfully traverse this objection.

Applicants acknowledge the Examiner's rejection of particular claims 1-20, under 35 U.S.C. § 112 ¶1, for lack of enablement. Applicants have amended independent claim 1 to obviate this objection.

Applicants acknowledge the Examiner's rejection of particular claims, under 35 U.S.C. § 102(a), (b) and (e), as allegedly being anticipated in view of alleged prior art (*Chen I*, claims claims 1-10 and 20; *Chen II*, claims claims 1-10 and 20; *Iacopetta*, claims 1-3, 5-8, 10 and 20; or *Hahnel*, claims 1-3, 5-8, 10 and 20). Applicants traverse this rejection based on applicants' present amendments of independent claim 1.

Applicants acknowledge the Examiner's rejection of claims 15-19, under 35 U.S.C. § 103(a), as being obvious over the alleged prior art (Chen I, Chen II, Iacopetta or Hahnel, each in view of Huang). Applicants traverse this rejection based on applicants' present amendments of independent claim 1.

The claims have been amended to conform with the restriction requirement.

No new matter has been added.

FORMALITIES

Restriction requirement. The claims have been amended to conform with the restriction requirement and pursuant election. No new matter has been added.

Priority. The Examiner states that original claims 1-10 and 15-20 are associated with a priority date corresponding to 02 April 2001, whereas original claims 11-14 are awarded the benefit of the date of the provisional filing (*i.e.*, 31 March 2000).

Sequence Listing. The Examiner has objected to the specification, under 35 U.S.C. 132 because it allegedly contains 'new matter' in view of the addition of SEQ ID NOS:66-76 in applicants' last amendment (Office Action of 16 November 2004, at page 4).

Specifically, the Examiner states that a Declaration is required to support inclusion of SEQ ID NO: 66 in the Sequence Listing.

Additionally, the Examiner alleges that there is no support for SEQ ID NO:67, a specific CpG island sequence within SEQ ID NO:66, because the 'cut-off'points (limits) or end positions of SEQ ID NO:67 were not specifically taught. Moreover the Examiner alleges that there is no support for SEQ ID NOS:68-71 (specific treated species of SEQ ID NO:67), because "CpG islands are not necessarily fully up or down methylated, and there is no such teaching in the specification" (Office Action at page 5).

Finally, the Examiner alleges that there is no support for the MYOD1 amplicon SEQ ID NO:72. Moreover the Examiner alleges that there is no support for SEQ ID NOS:73-76 (specific fully up-methylated and fully down-methylated treated species of SEQ ID NO:72) (*Id*).

Applicants respectfully traverse these objections, based on the fact that the sequences are in fact supported by the originally filed specification.

Specifically, with respect to SEQ ID NO:66, applicants are obtaining signatures on the required Declaration.

Additionally, with respect to SEQ ID NO:67, applicants' originally-filed disclosure teaches multiple species of a genus of sequences that are sufficiently defined and described by (i) the accession number and (ii) the CpG island definition/formula (specification pages 7-8). SEQ ID NO:67 is but one taught species that falls within this genus. All possible 'cut-off'points (limits) or end positions of CpG islands within SEQ ID NO:67 are taught and disclosed by virtue of the teaching of accession number and the associated CpG definition/formula.

With respect to SEQ ID NOS:68-71, the specification fully supports the specific fully up-methylated or fully down-methylated treated species of SEQ ID NO:67. Specifically, the specification (at page 21 ll. 18-35) teaches the design and use of sets of fully up-methylated and fully down-methylated primers. Significantly, the primers, regardless of the amplification position along SEQ ID NO:67, must be complementary to the strands of the corresponding (*i.e.*, fully up or down methyled strands) bisulfite-treated DNA. Thus, teachings of the specific fully up and fully down-methylated primers are integral with teaching of the complementary fully up and down methylated treated DNA strands is integral. Therefore, the specification does in fact teach SEQ ID NOS:68-71, and it is irrelevant that MYOD1 genomic islands are not necessarily fully up or fully down methyled (as stated by the Examiner). The fact that MYOD1 genomic islands are not necessarily fully up or fully down methyled does not mean that applicants cannot teach (as was done) the exemplary specific fully up-, and down-methylated species of SEQ ID NOS:68-71.

With respect to SEQ ID NO:72, the specification (at page 30, Table II, 5th column from left in the MYOD1 row), explicitly teaches the amplicon of SEQ ID NO:72 by providing the amplicon end-points within the MYOD1 gene. Moreover, the primers and probe disclosed in this row teach that the amplicon is of bisulfite-treated sequences. Futhermore, as described above for SEQ ID NOS:68-71, the specification does in fact teach SEQ ID NOS:73-76,

Applicants thus respectively request that his objection be withdrawn.

Rejection under 35 U.S.C. § 112 ¶1

Claims 1-20 were rejected by the Examiner, under 35 U.S.C. § 112 ¶1, for lack of enablement (Office Action of 16 November 2004, at page 6).

Specifically, the Examiner alleges that the specification, while supporting diagnosis and prognosis of Barrett's esophagus and esophageal cancer using esophageal tissue samples, does not support diagnosis and prognosis of any cancer using any tissue sample (Office Action at pages 6-11),

Applicants have responsively amended independent claim 1 to obviate the Examiner's concern. Specifically, claim 1 has been amended to recite "obtaining a esophageal tissue sample comprising genomic DNA" and further recite "determining, based at least in part upon the methylation state of the at least one genomic CpG sequence, a diagnosis or prognosis of esophageal cancer or an esophageal cancer-related condition."

Applicants, therefore, respectfully request withdrawal of the Examiner's rejection of claims 1-20, under 35 U.S.C. § 112 ¶1, in view of applicants above described claim amendments.

Rejections under 35 U.S.C. § 102

Iacopetta

Claims 1-3, 5-8, 10 and 20 were rejected by the Examiner, under 35 U.S.C. § 102(b) as being anticipated by Iacopetta (Iacopetta et al., *Int. J. of Cancer*, 17:429-432 (1997)) (Office Action of 16 November 2004, at page 12).

Specifically, the Examiner alleges that Iacopetta teaches regional hypermethylation of a 3' downstream region of MYOD1 in relation to colorectal neoplasia, and thus teaches diagnosis or prognosis thereof. The Examiner further states that the present claims have been "interpreted to encompass the gene that can be analyzed by the recited SEQ ID NOS in the claim." but that they "do not require analysis with the specifically recited SEQ ID NOS" (*Id*, page 13).

Applicants respectfully request withdrawal of this 35 U.S.C. § 102(b)-based rejection of claims 1-3, 5-8, 10 and 20, based on applicants' above described amendments to independent claim 1.

Hahnel

Additionally, claims 1-3, 5-8, 10 and 20 were rejected by the Examiner, under 35 U.S.C. § 102(b) as being anticipated by Hahnel (Hahnel et al., *Anticancer Research*, 16:2111-2116 (1996)) (Office Action of 16 November 2004, at page 13).

Specifically, the Examiner alleges that Hahnel teaches making a diagnostic or prognostic prediction of breast cancer based at least in part on the methylation state of a 3' downstream region of MYOD1.

Applicants respectfully request withdrawal of this 35 U.S.C. § 102(b)-based rejection of claims 1-3, 5-8, 10 and 20, based on applicants' above described amendments to independent claim 1.

Chen I

Additionally, claims 1-10 and 20 were rejected by the Examiner, under 35 U.S.C. § 102(b) as being anticipated by Chen (Chen et al., *American Journal of Pathology*, 152:1071-1079 (1998)) (Office Action of 16 November 2004, at page 14).

Specifically, the Examiner alleges that Chen teaches making a diagnostic or prognostic prediction of rhabdomysarcomas based at least in part on the methylation state (partial methylation or hypomethylation) of a 5' upstream (*e.g.*, promoter) region of MYOD1.

Applicants respectfully request withdrawal of this 35 U.S.C. § 102(b)-based rejection of claims 1-3, 5-8, 10 and 20, based on applicants' above described amendments to independent claim 1.

Chen II

Additionally, Claims 1-10 and 20 were rejected by the Examiner, under 35 U.S.C. § 102(a) and (e) as being anticipated by Chen II (Bin Chen; U.S. Patent No. 6,180,344; issued January 30, 2001) (Office Action of 16 November 2004, at page 16).

Specifically, the Examiner alleges that Chen II teaches making a diagnostic or prognostic prediction of embryonal rhabdomysarcomas based at least in part on the methylation state (hypomethylation) of a 5' upstream (*e.g.*, promoter) region of MYOD1.

Applicants respectfully request withdrawal of this 35 U.S.C. § 102(b)-based rejection of claims 1-3, 5-8, 10 and 20, based on applicants' above described amendments to independent claim 1.

Rejections under 35 U.S.C. § 103

Chen I, Chen II, Iacopetta or Hahnel, in view of Huang

Claims 15-19 were rejected by the Examiner, under 35 U.S.C. § 103(a), as being obvious over the alleged prior art (*i.e.*, Chen I, Chen II, Iacopetta or Hahnel, as cited above, each in view of Huang (Huang et al., *Human Molecular Genetics*, 8:459-470, 1999)) (Office Action of 16 November 2004, at page 17).

Specifically, the Examiner asserts that: Chen I and Chen II teach correlation of partial and *hypo*methylation of MYOD1 with particular rhabdomyosarcomas; that Chen I teaches the same MYOD1 accession number as presently disclosed by applicants; that Iacopetta teaches correlation of *hyper*methylation of a 3' downstream region of MYOD1 with colorectal tumors; that Hahnel teaches correlation of *hyper*methylation of a 3' downstream region of MYOD1 with breast cancer; that neither Chen I, Chen II, Iacopetta nor Hahnel teach analysis of methylation alteration with DMH; but that Huang et al teach analysis of methylation status with DMH (an array based method); and therefore that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to improve the analysis methods of Chen I or II or Iacopetta or Hahnel, with the DMH analysis of Huang.

However, a *prima facie* case of obvious cannot be made for the claims as presently amended, because none of the asserted art, alone or in combination teach or otherwise suggest prognosis or diagnosis of esophageal cancer or esophageal cancer-related conditions (*e.g.*, Barrett's esophagus) by analysis of MYOD1 methylation status.

Applicants respectfully request withdrawal of this 35 U.S.C. § 103(a)-based rejection of claims 15-19, based on applicants' above described amendments to independent claim 1.

CONCLUSION

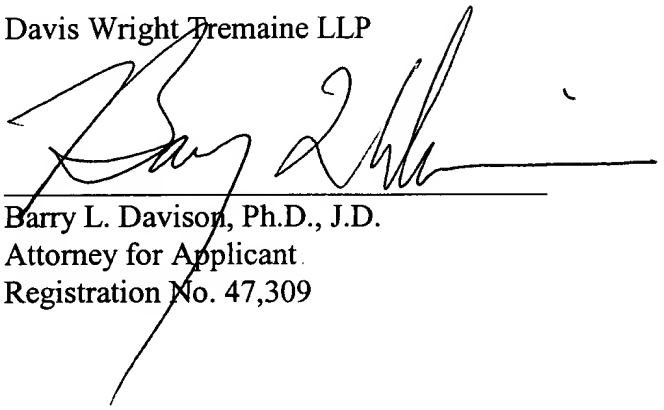
In view of the foregoing amendments and remarks, applicants respectfully request entry of the present Response and Amendment, and allowance of all claims 1-20.

The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

No new matter has been added.

Respectfully submitted,

Davis Wright Tremaine LLP



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